

**CYCLOOCTA[b][1,4]DIAZEPINO[6,7,1-hi]INDOLES AND DERIVATIVES**

This application claims priority from copending provisional application Serial Number 60/245,602, filed November 3, 2000, the entire disclosure of which is hereby  
5 incorporated by reference.

The present invention relates to cycloocta[b][1,4]diazepino[6,7,1-hi]indoles and derivatives thereof, which are serotonin 5-hydroxytryptamine <sub>2c</sub> (5HT<sub>2c</sub>) receptor agonists useful for the treatment of disorders, such as obsessive-compulsive disorder,  
10 depression, anxiety, generalized anxiety disorder, schizophrenia, migraine, sleep disorders, eating disorders, obesity, epilepsy, and spinal cord injury.

**BACKGROUND OF THE INVENTION**

15 Obesity is a medical disorder characterized by an excess of body fat or adipose tissue. Comorbidities associated with obesity are Type II diabetes, cardiovascular disease, hypertension, hyperlipidemia, stroke, osteoarthritis, sleep apnea, gall bladder disease, gout, some cancers, some infertility, and early mortality. As the percentage of obese individuals continues to rise both in the U.S. and abroad, obesity is expected to  
20 be a major health risk in the 21<sup>st</sup> Century. The serotonin 5-hydroxytryptamine (5-HT) receptor is a G-protein coupled receptor which is expressed in neurons in many regions of the human central nervous system. [Wilkinson, L. O. and Dourish, C. T. in *Serotonin Receptor Subtypes: Basic and Clinical Aspects* (ed. Peroutka, S. J. ) 147-210 (Wiley-Liss, New York, 1991).] The 5HT<sub>2c</sub> receptor (formerly called the 5HT<sub>1c</sub> receptor) is a  
25 prominent subtype of the serotonin receptor found in the central nervous system of both rats and humans. It is expressed widely in both cortical and subcortical regions. [Julius, D. MacDermott, A. B., Axel, R. Jessell, T. M. *Science* 241:558-564 (1988).] Studies in several animal species and in humans have shown that the non-selective 5HT<sub>2c</sub> receptor agonist, *meta*-chlorophenylpiperazine (MCP) decreases food intake. [Cowen,  
30 P.J., Clifford, E. M. , Williams, C., Walsh, A. E. S., Fairburn, C. G. *Nature* 376: 557 (1995).] Tecott, *et al* have demonstrated that transgenic mice lacking the 5HT<sub>2c</sub> receptor eat more and are heavier than Wild Type mice. [Tecott, L. H., Sun, L. M., Akana, S. F., Strack, A. M., Lowenstein, D. H., Dallman, M. F., Jullus, D. *Nature* 374: 542-546 (1995).] Compounds of this invention are 5HT<sub>2c</sub> receptor subtype selective

agonists which are selective over other monoamine receptors, causes a reduction in food intake and result in a reduction in weight gain. Other therapeutic indications for 5HT<sub>2C</sub> agonists are obsessive compulsive disorder, depression, panic disorder, schizophrenia, sleep disorders, eating disorders, epilepsy, and spinal cord injury.

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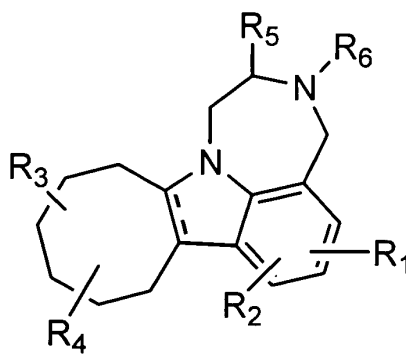
United States Patent 3,914,250 (October 21, 1975) describes 1,4-diazepino[6,5,4-jk]carbazoles as anticonvulsant agents. The compounds of this invention are not carbazoles. This invention relates to cycloocta[b][1,4]diazepino[6,7,1-hi]indoles and derivatives which bind to and activate 5HT<sub>2C</sub> receptors in the CNS and are useful for the treatment of CNS disorders which can benefit from modulation of the 5HT<sub>2C</sub> receptor.

10

### DESCRIPTION OF THE INVENTION

15

This invention provides compounds of formula I having the structure



I

wherein:

R<sub>1</sub> and R<sub>2</sub> are each independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, fluorinated alkyl of 1-6 carbon atoms, -CN, -NH-SO<sub>2</sub>-alkyl of 1-6 carbon atoms, -SO<sub>2</sub>-NH-alkyl of 1-6 carbon atoms, alkyl amide of 1-6 carbon atoms, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, fluorinated alkoxy of 1-6 carbon atoms, acyl of 2-7 carbon atoms, or aroyl;

25

$R_3$ ,  $R_4$  are each independently hydrogen,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_7$  cycloalkyl or  $-CH_2-C_3-C_7$  cycloalkyl;

$R_5$  is hydrogen or  $C_1$ - $C_6$  alkyl;

$R_6$  is hydrogen or  $C_1$ - $C_6$  alkyl; and

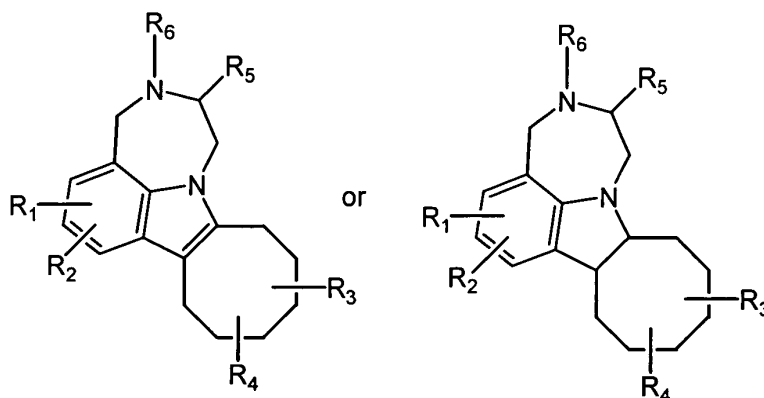
5 wherein the dashed line indicates an optional double bond;

or a pharmaceutically acceptable salt thereof.

In the definitions of  $R_1$  and  $R_2$  herein, the fluorinated alkyl and fluorinated alkoxy groups indicate the specified alkyl or alkoxy groups having any amount of fluorine substitution including, but not limited to, groups such as  $-CHF_2$ ,  $-CF_3$ ,  $-C_2F_5$ ,  $-OCF_3$ , etc.

The dashed line in formula I indicates an optional double bond, indicating the optional reduction described above.

15 One group of compounds of this invention comprises those of the formulae:



wherein

$R_1$  and  $R_2$  are each independently selected from hydrogen, alkyl of 1-6 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, trifluoromethyl,  $-CN$ , amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl moiety, or trifluoromethoxy;

$R_3$ ,  $R_4$  are each independently hydrogen or  $C_1$ - $C_6$  alkyl;

$R_5$  is hydrogen or  $C_1$ - $C_6$  alkyl;

25  $R_6$  is hydrogen or  $C_1$ - $C_6$  alkyl; or a pharmaceutically acceptable salt thereof.

Another group of compounds of this invention comprises those in which each of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from H or alkyl of 1-6 carbon atoms, or a pharmaceutically acceptable salt thereof.

5           The 5HT<sub>2C</sub> receptor agonists of this invention are useful for the treatment or prevention in mammals, preferably in humans, of disorders involving the central nervous system such as obsessive-compulsive disorder, depression, atypical depression, bipolar disorders, anxiety, generalized anxiety disorder, schizophrenia, psychoses, personality disorders, organic mental disorders, behavioral disorders associated with dementia or  
10 age-related conditions, aggressivity, drug and alcohol addiction, social phobias, sexual dysfunction, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, bulimia or anorexia nervosa, obesity, epilepsy, and premenstrual tension..

15           This invention also includes methods of utilizing the compounds herein in treatments or preventive regimens for treatment of central nervous system deficiencies associated with trauma, stroke, neurodegenerative diseases or toxic or infective CNS disorders including, but not limited to, encephalitis or meningitis; or cardiovascular disorders, including thrombosis; gastrointestinal disorders such as malfunction of  
20 gastrointestinal motility; and diabetes insipidus. These methods include the improvement or inhibition of further degradation of central nervous system activity during or following the malady or trauma in question. Included in these improvements are maintenance or improvement in motor and motility skills, control, coordination and strength.

25           These methods of this invention comprise administering to a mammal in need thereof a pharmaceutically or therapeutically effective amount of a compound of this invention, or a pharmaceutically acceptable salt thereof.

30           The compounds of this invention contain asymmetric carbon atoms and thus give rise to optical isomers and diastereoisomers. While shown without respect to stereochemistry in Formula I, the present invention includes such optical isomers and diastereoisomers; as well as the racemic and resolved, enantiomerically pure R and S

stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

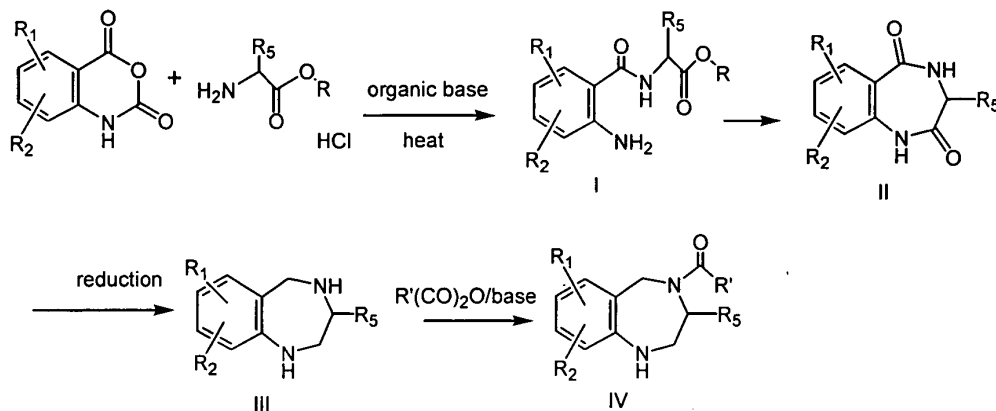
The term "alkyl" includes both straight- and branched-chain saturated aliphatic hydrocarbon groups and cycloalkyl groups. Halogen is defined as Cl, Br, F, and I. The term "aroyl" is defined as an aryl ketone, where aryl is defined as an aromatic system of 6-14 carbon atoms, which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. Preferred aryl groups include phenyl, thiophenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl groups.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids.

Preferred compounds of this invention are those in which R is hydrogen. Especially preferred are compounds which are enantiomerically pure stereoisomers of compounds where R is hydrogen and the indole ring is reduced or not reduced.

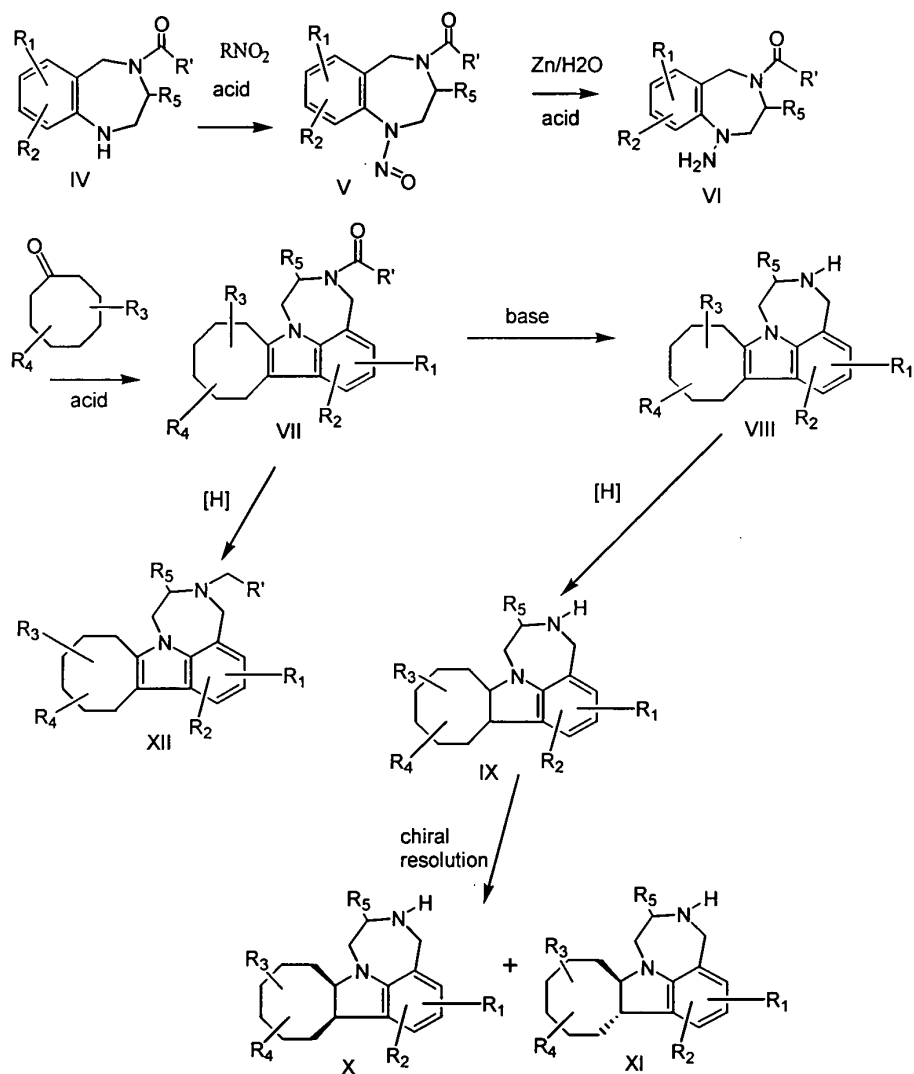
The compounds of this invention can be prepared according to the following scheme from commercially available starting materials or starting materials which can be prepared using literature procedures. **Scheme 1** shows the preparation of a key intermediate and **Scheme 2** shows the preparation of representative compounds of this invention.

Scheme 1



- According to **Scheme 1**, a substituted or unsubstituted isatoic anhydride is allowed to react with substituted or unsubstituted glycine hydrochloride or an ester of the same in an organic base such as pyridine or triethylamine, to give either open-chain intermediate I or the benzodiazepinedione II. Intermediate I can be converted to intermediate II by heating in the presence of an acid, such as acetic acid. The benzodiazepinedione II is reduced to the benzodiazepine III using a reducing agent such as lithium aluminum hydride or a borane-tetrahydrofuran complex. The secondary nitrogen atom in III is protected using a protecting group, such as an amide by reacting III with an acylating agent, such as acetic anhydride, in the presence of a base, such as triethylamine, to give an acylated benzodiazepine IV.

Scheme 2



According to Scheme 2, Intermediate IV is allowed to react with a nitrosating agent, such as sodium nitrite, in the presence of an acid, such as acetic acid, to give nitroso compounds V. The nitroso compounds are reduced to hydrazines VI using a reducing agent, such as zinc powder in acetic acid and water. The hydrazines VI are allowed to react with substituted or unsubstituted cyclooctanones in acid, such as acetic acid, to give the fused indoles VII. The fused indoles VII can be treated with a base, such as NaOH, in a polar solvent, such as water or an alcohol, or with an acid, such as

hydrochloric acid, to give the fused indoles **VIII**, which are products of this invention. In addition, fused indoles **VIII** can be reduced, with a reducing agent, such borane in THF, in the presence of an acid, such as trifluoroacetic acid, to give fused indolines **IX** which are products of this invention. Fused indolines **IX** are diastereoisomeric mixtures that can be resolved using chiral HPLC or chiral resolving agents to give stereo isomers **X** and **XI** and enantiomers thereof, which are products of this invention. Also, compounds **VII** can be reduced with reducing agents, such as a borane-THF complex, to give **XII** which are compounds of this invention.

10 The acylation steps of this invention are understood to include reactions of the appropriate compound with any acylating agent and reaction conditions known in the art. Useful in these steps are acylating agents include acid halides and esters or anhydrides of the appropriate aliphatic carboxylic acid. Useful acid halides include acetyl chloride, propionyl chloride, isobutyryl chloride, benzoyl chloride, etc. Acid anhydrides include 15 acetic anhydride and benzoic anhydride. Similarly, alkylation steps herein are understood to include any relevant alkylating agents and conditions known in the art. These include, but are not limited to the use of alkyl halides, such as methyl iodide, or alkyl tosylates or aldehyde alkylating agents in the presence of an applicable reducing agent.

20 Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, 25 camphorsulfonic, and similarly known pharmaceutically acceptable acids. The processes herein will be understood to include an optional additional step of forming a salt form of the products via standard addition reactions with any pharmaceutically acceptable organic or inorganic acid.

30 The ability of the compounds of this invention to act as 5HT<sub>2C</sub> agonists was established in several standard pharmacological test procedures; the procedures used and results obtained are provided below.



## **Test Procedures**

### **5HT<sub>2C</sub> Receptor Binding Test Procedure**

To evaluate high affinity for the 5HT<sub>2C</sub> receptor, a CHO (Chinese Hamster Ovary) cell line transfected with the cDNA expressing the human 5-hydroxytryptamine<sub>2C</sub> (h5HT<sub>2C</sub>) receptor was maintained in DMEM (Dulbecco's Modified Eagle Media) supplied with fetal calf serum, glutamine, and the markers: guaninephosphoribosyl transferase (GTP) and hypoxanthinethymidine (HT). The cells were allowed to grow to confluence in large culture dishes with intermediate changes of media and splitting. Upon reaching confluence, the cells were harvested by scraping. The harvested cells were suspended in half volume of fresh physiological phosphate buffered saline (PBS) solution and centrifuged at low speed (900 x g). This operation was repeated once more. The collected cells were then homogenized with a polytron at setting #7 for 15 sec in ten volumes of 50 mM Tris.HCl, pH 7.4 and 0.5 mM EDTA. The homogenate was centrifuged at 900 x g for 15 min to remove nuclear particles and other cell debris. The pellet was discarded and the supernatant fluid recentrifuged at 40,000 x g for 30 min. The resulting pellet was resuspended in a small volume of Tris.HCl buffer and the tissue protein content was determined in aliquots of 10-25 microliter (μl) volumes. Bovine Serum Albumin (BSA) was used as the standard in the protein determination by the method of Lowry et al., (J. Biol. Chem., 193:265 (1951). The volume of the suspended cell membranes was adjusted with 50 mM Tris.HCl buffer containing: 0.1% ascorbic acid, 10 mM pargyline and 4 mM CaCl<sub>2</sub> to give a tissue protein concentration of 1-2 mg per ml of suspension. The preparation membrane suspension (many times concentrated) was aliquoted in 1ml volumes and stored at -70 C until used in subsequent binding experiments.

Binding measurements were performed in a 96 well microtiter plate format, in a total volume of 200 μl. To each well was added: 60 μl of incubation buffer made in 50 mM Tris.HCl buffer, pH 7.4 and containing 4 mM CaCl<sub>2</sub>; 20 μl of [<sup>125</sup>I] DOI (S.A., 2200 Ci/mmol, NEN Life Science).

The dissociation constant, K<sub>D</sub> of [<sup>125</sup>I] DOI at the human serotonin 5HT<sub>2C</sub> receptor was 0.4 nM by saturation binding with increasing concentrations of [<sup>125</sup>I] DOI. The reaction was initiated by the final addition of 100.0 μl of tissue suspension containing 50 μg of receptor protein. Nonspecific binding is measured in the presence

of 1  $\mu$ M unlabeled DOI added in 20.0  $\mu$ l volume. Test compounds were added in 20.0 ml. The mixture was incubated at room temperature for 60 min. The incubation was stopped by rapid filtration. The bound ligand-receptor complex was filtered off on a 96 well unfilter with a Packard <sup>®</sup> Filtermate 196 Harvester. The bound complex caught on  
 5 the filter disk was dried in a vacuum oven heated to 60° C and the radioactivity measured by liquid scintillation with 40  $\mu$ l Microscint-20 scintillant in a Packard TopCount<sup>®</sup> equipped with six (6) photomultiplier detectors.

Specific binding is defined as the total radioactivity bound less the amount bound in the presence of 1  $\mu$ M unlabeled DOI. Binding in the presence of varying  
 10 concentrations of test drugs is expressed as percent of specific binding in the absence of drug. These results are then plotted as log % bound vs log concentration of test drug. Non linear regression analysis of data points yields both the IC50 and the Ki values of test compounds with 95% confidence limits. Alternatively, a linear regression line of decline of data points is plotted, from which the IC50 value can be read off the curve and  
 15 the Ki value determined by solving the following equation:

$$K_i = \frac{IC_{50}}{1 + L/KD}$$

20 where L is the concentration of the radioactive ligand used and the KD is the dissociation constant of the ligand for the receptor, both expressed in nM.

The following Ki's are provided for various reference compounds:

Ki value and 95% confidence interval.

25	Ritanserin	2.0 (1.3 - 3.1) nM
	Ketanserin	94.8 (70.7 - 127.0) nM
	Mianserin	2.7 (1.9 - 3.8) nM
	Clozapine	23.2 (16.0 - 34.0) nM
	Methiothepin	4.6 (4.0 - 6.0) nM
30	Methysergide	6.3 (4.6 - 8.6) nM
	Loxapine	33.0 (24.0 - 47.0) nM
	mCPP	6.5 (4.8 - 9.0) nM
	DOI	6.2 (4.9 - 8.0) nM

Stimulation of [ $^3\text{H}$ ] Inositol Monophosphate production by 5HT<sub>2C</sub> agonists.

CHO cells transfected with the cDNA expressing the human 5-HT<sub>2C</sub> receptor were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum and non-essential amino acids. Upon reaching confluence the cells were harvested using PBS/EDTA and plated in 24 well plates at an initial density of  $2.5 \times 10^5$  cells per well. One (1) ml of maintenance medium containing 1  $\mu\text{Ci/ml}$  myo-[ $^3\text{H}$ ] inositol was added to each well. After 48 hours labeling, the cells were washed once with 0.5 ml DMEM containing 25 mM HEPES and 10 mM LiCl, then preincubated with the medium for 30 min (antagonists were included in this period if tested). At the end of the preincubation, the medium was removed, the cells were then incubated with test compounds (in presence of antagonists if needed) for 30 min. The reaction was terminated by removal of the incubation solution and addition of 0.5 ml ice-cold 5% PCA, followed by 15 to 30 min incubation on ice. 200  $\mu\text{l}$  of 0.5 M Tes/1.5 M K<sub>2</sub>CO<sub>3</sub> was added to each well to neutralize to pH 7, and plates were left on ice for another 15 to 30 min to precipitate all salts. The liquid and solid phases were separated by centrifugation.

A portion (350  $\mu\text{l}$ ) of the upper aqueous phase was applied to Dowex AG-1X8 (formate form, 100-200 mesh) columns. The columns were then washed stepwise with 10 ml of water and 10 ml of 25 mM ammonium formate to remove free myo-[ $^3\text{H}$ ]inositol and deacylated phosphoinositol, respectively. Finally 10 ml of 0.2 M ammonium formate solution was applied to the columns to elute [ $^3\text{H}$ ] inositol monophosphate ([ $^3\text{H}$ ] IP<sub>1</sub>) directly into scintillation vials. Of this eluate, 1 ml was used to determine radioactivity by scintillation counting.

Agonist-stimulated levels of [ $^3\text{H}$ ]inositol monophosphate (IP<sub>1</sub>) is expressed as a percentage of the response observed with a maximally effective concentration of 5-HT (10  $\mu\text{M}$ ). A 3-parameter logistic function is used to generate estimate of EC<sub>50</sub>/IC<sub>50</sub>. Antagonists are tested in the presence of 10  $\mu\text{M}$  5-HT.

The following data are provided for various reference compounds:

5-HT	15.1 nM	EC <sub>50</sub>
mCPP	46.8 nM	EC <sub>50</sub>
	60%	E <sub>MAX</sub> (relative to 5-HT)
SB200646	286 nM	IC <sub>50</sub> (10μM 5-HT as agonist)

5

**Results**Results from in vitro Test Procedures

Compound	5HT <sub>2C</sub> Affinity DOI/Agonist binding (K <sub>i</sub> , nM)	5HT <sub>2C</sub> % Emax (5HT, 100%)	Stimulation of IP3 (EC <sub>50</sub> , nM)
Example 1	16	120	165
Example 2	65		

10           The results obtained in this standard pharmacological test procedures demonstrate that the compounds of this invention are 5HT<sub>2C</sub> receptor agonists useful for the treatment of diseases involving the central nervous system such as obsessive-compulsive disorder; depression; anxiety; generalized anxiety disorder, panic disorder; schizophrenia; migraine; sleep disorders, such as sleep apnea; eating disorders, such as hyperphagia; obesity; epilepsy, and spinal cord injury.

15           This invention also comprises pharmaceutical compositions comprising a pharmaceutically or therapeutically effective amount of one or more compounds of this invention, or a pharmaceutically acceptable salt thereof, and one or more  
20   pharmaceutical carriers or excipients. The compounds of this invention can be formulated neat or with a pharmaceutical carrier for administration, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmacological practice. The pharmaceutical carrier may be solid or liquid.

25

          A solid carrier can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an

encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably  
 5 contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

10 Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers,  
 15 buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g. glycols)  
 20 and their derivatives, lethicins, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are useful in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable  
 25 propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds of this  
 30 invention can also be administered orally either in liquid or solid composition form.

The compounds of this invention may be administered rectally or vaginally in the form of a conventional suppository. For administration by intranasal or intrabronchial inhalation or insufflation, the compounds of this invention may be formulated into an

aqueous or partially aqueous solution, which can then be utilized in the form of an aerosol. The compounds of this invention may also be administered transdermally through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semipermeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

As used herein, the terms "pharmaceutically effective amount" or "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, prevention or amelioration of the cause or symptoms of the malady or condition, or an increase in rate of treatment, prevention or amelioration of such conditions. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

The dosage requirements vary with the particular compositions employed, the route of administration, the severity of the symptoms presented and the particular subject being treated. Daily dosages of active compound would be 0.02  $\mu\text{g/kg}$  - 750  $\mu\text{g/kg}$ . Treatment will generally be initiated with small dosages less than the optimum dose of the compound. Thereafter the dosage is increased until the optimum effect under the circumstances is reached; precise dosages for oral, parenteral, nasal, or intrabronchial administration will be determined by the administering physician based on experience with the individual subject treated. Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active

ingredient; the unit dosage forms can be packaged compositions, for example, packaged powders, vials, ampoules, pre filled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

5

The following provides the preparation of compounds representative of this invention.

### Example 1

10

#### 1,2,3,4,8,9,10,11,12,13-Decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole

#### **Intermediate A. 4-Acetyl-2,3,4,5-tetrahydro-1H-benzodiazepine**

Acetic anhydride (0.60 mL) was added dropwise to a stirred suspension of  
15 2,3,4,5-tetrahydro-1H-benzodiazepine (950 mg, 6.4 mmol) in anhydrous ether (25 mL). After refluxing for four hours, the reaction mixture was filtered to remove a solid. Evaporation of the filtrate gave a residue which was purified by chromatography on silica gel eluting with 5% methanol in ethyl acetate. Evaporation of the product fractions gave an oil. The solid removed by filtration above contained a mixture of starting material and  
20 product by thin layer chromatography. The solid was partitioned between water and methylene chloride to remove salts and the organic portion was purified on silica gel as described above. Evaporation of the product fractions gave the product as an oil. Both product oils were dried under oil pump vacuum and gradually solidified. The first crop of intermediate A. (322 mg) melted at 83-85 °C (lit. mp: 84-86 °C recrystallized from  
25 ether). The second crop of intermediate A (450 mg) isolated from the solid, melted at 75-79 °C.

Anal. Calcd. for  $C_{11}H_{14}N_2O$

Theory: %C, 69.44; %H, 7.42; %N, 14.73

30 Found: %C, 69.6; %H, 7.52; %N, 14.71

Intermediate A (5 g) was partially dissolved in water (50 mL) containing conc. HCl (3 mL) while chilling in an ice/water bath. The ice bath was removed and a solution

of  $\text{NaNO}_2$  (1.8 g) dissolved in water (5 mL) was added dropwise with stirring over 20 min. The reaction mixture was extracted into methylene chloride, dried ( $\text{MgSO}_4$ ), filtered and evaporated to give an oil which was dissolved in glacial acetic acid (70 mL). Powered zinc (6.25 g) was added portionwise at 20-26°C (exotherm) and the mixture  
5 was allowed to stir an additional hour after the addition of zinc was complete. The reaction mixture was filtered into a flask containing cyclooctanone (7 g) and was heated at 110-120°C for 3 h. The acetic acid was removed by evaporation under reduced pressure and the residue was partitioned between 2.5 N NaOH and ethyl acetate. The ethyl acetate was removed by evaporation under reduced pressure and the residue was  
10 purified by column chromatography on silica gel eluting with 0.3% - 0.8% methanol in methylene chloride to give 3-acetyl-1,2,3,4,8,9,10,11,12,13-decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole (1.51 g), mp: 41-44°C

Anal. Calcd. For  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O} \cdot 0.5 \text{H}_2\text{O}$

15 Theory: %C, 74.72; %H, 8.25; %N, 9.19  
Found: %C, 74.59; %H, 8.1; %N, 8.96

3-Acetyl-1,2,3,4,8,9,10,11,12,13-decahydrocycloocta[b][1,4]diazepino[6,7,1-hi]indole (1.3 g) was dissolved in methanol and diluted with 2.5N NaOH and excess solid  
20 NaOH was added. The solution was heated at 95 °C overnight. The volatiles were evaporated under reduced pressure and the residue was partitioned between water and ethyl acetate. The organic phase was separated and evaporated and the residue was purified by chromatography on silica gel eluting with 3-4% methanol in methylene chloride to give a colorless oil. The oil was treated with 4 N HCl with stirring and  
25 warming. The precipitate that formed was isolated by filtration, triturated with ethanol, and allowed to stand overnight. A yellow solid was isolated by filtration and dried to give the hydrochloride salt of the title compound (683 mg), mp: 316-318 °C

Anal. Calcd. For  $\text{C}_{17}\text{H}_{22}\text{N}_2 \cdot \text{HCl}$

30 Theory: %C, 70.21; %H, 7.97; %N, 9.63  
Found: %C, 70.2; %H, 7.65; %N, 9.57



**Example 2****1,2,3,4,7b,8,9,10,11,12,13,13a-Dodecahydrocycloocta[b][1,4]diazepino[6,7,1-h]indole**

The product of Example 1 (370 mg, 1.45 mmol) was dissolved in trifluoroacetic acid (10 mL) under a nitrogen atmosphere and cooled in an ice/water bath. 1.5 M BH<sub>3</sub> in THF (7 mL) was added over 4 minutes. The cooling bath was removed and the reaction mixture was stirred for an additional 45 min. The reaction was quenched by the careful addition of water. Then 2.5 N NaOH was added followed by 50% aqueous NaOH until the reaction mixture remained basic. The product was extracted into methylene chloride and was purified on silica gel eluting with 3-15% methanol in methylene chloride. Evaporation of the volatiles under reduced pressure gave an oil which crystallized to give the title compound as a yellow solid (238 mg), mp: 58-63 °C.

Anal. Calcd for C<sub>17</sub>H<sub>24</sub>N<sub>2</sub> • 0.4 H<sub>2</sub>O

Calcd: %C, 77.46; %H, 9.48; %N, 10.63.

Found: %C, 77.48; %H, 9.29; %N, 10.54..